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AN INTERNATIONAL STUDY OF SMOKING AND BLADDER CANCER

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ABSTRACT

The effects of smoking cigarettes and other forms of tobacco on the development of cancer of the lower urinary tract (bladder cancer) were evaluated in Boston, Massachusetts, Manchester, United Kingdom and Nagoya, Japan. Population-based series of incident cases and controls were identified and interviewed in each area. The present analyses were based on 592 cases and 533 controls in Boston, 553 cases and 731 controls in Manchester, and 290 cases and 588 controls in Nagoya. Smokers of cigarettes had about twice the incidence of bladder cancer as nonsmokers. In men the strength of the association between cigarette smoking and bladder cancer was similar in the 3 study areas. The strength of the association varied somewhat from area to area among women. Bladder cancer risk increased with frequency of cigarette smoking and with deep inhaling. In Boston men who smoked 2 or more packs of cigarettes per day and inhaled deeply had nearly 7 times the risk of nonsmokers. Ex-smokers had a level of risk between that of current smokers and nonsmokers. However, there was no clear relationship between risk and age at which cigarette smoking began, time since discontinuation among ex-smokers and use of filters. Over-all, there was little difference in bladder cancer risk between men who had and who had not smoked pipes but pipe smoking did appear to be associated with risk among men who had never smoked cigarettes. Cigar smoking was unrelated to bladder cancer.

The existence of a positive association between cigarette smoking and the development of cancer of the lower urinary tract (bladder cancer) is generally accepted. The best documented features of this association are its over-all size (a relative risk of about 2 to 3) and its increase in strength with increasing intensity of smoking (packs per day).[1-11] Other aspects of the relationship between smoking and bladder cancer risk have received less attention and are not well understood. These issues include the relation of risk to duration of cigarette smoking, discontinuation of the habit, use of filter cigarettes, use of pipes and cigars, and smoking in diverse environmental settings. We did a collaborative case-control study of bladder cancer that offered an opportunity to address these questions.

METHODS

The study was done in Greater Boston, Massachusetts, part of Greater Manchester County, United Kingdom and metropolitan Nagoya, Japan. The study methods have been described in detail.[12,13] Briefly, an attempt was made to assemble a complete series of incident cases in each area during the respective study period (March 1976 through May 1977 in Boston, October 1976 through September 1978 in Manchester and January 1976 through December 1978 in Nagoya). Case identification was accomplished primarily through hospitals. To be eligible a patient had to have had an initial diagnosis of a primary neoplasm of the lower urinary tract (bladder, ureter, renal pelvis or urethra) during the study period, and had to be at least 21 years old and a resident of the study area at the time of diagnosis. Patients ≧90 years old at the time of diagnosis were not eligible for interview. Tumors throughout the histologic spectrum from papilloma to invasive neoplasia were included. There were 741 patients <90 years old identified in Boston, 577 in Manchester and 348 in Nagoya. Of the tumors 95 per cent occurred in the bladder and 83 per cent were specified in the records as squamous or transitional cell carcinoma. A centralized pathology review indicated that virtually every case in this study had a transitional or squamous tumor.[14] For brevity the term bladder cancer is used as a synonym for neoplasms of the lower urinary tract.[12]

Controls were selected from electoral registers available in each study area. The sampling methods ensured that the control series would have an age and sex distribution similar to that of the respective series of cases. There were 677 controls selected in Boston, 817 in Manchester and 735 in Nagoya.

Subjects were interviewed according to a standardized schedule. If a subject was too ill for interview, could not be contacted or was dead an attempt was made to interview a relative or friend familiar with the subject's background and habits. In Boston and Manchester most interviews were done at the home of the subject. In Nagoya most controls were interviewed at home but the majority of patients were interviewed while hospitalized or during outpatient visits.[13] Interviews were obtained for 597 cases (81 per cent of the total eligible) and 544 controls (80 per cent) in Boston, 555 cases (96 per cent) and 735 controls (90 per cent) in Manchester, and 293 cases (84 per cent) and 589 controls (80 per cent) in Nagoya.

The interview included questions on many known or suspected causes of bladder cancer.[12] Questions on current exposure referred to experience 1 year before interview or in the calendar year before hospitalization for cases interviewed >1 year after initial admission. With respect to smoking habits, subjects were asked first whether they had ever smoked ciga-

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rettes. Those who answered yes were asked how much they had smoked on the average while they were smokers, when they began smoking cigarettes, the period during which they smoked the most and how much they had smoked then, the current amount smoked and, if they no longer smoked, when they had stopped. Periods of temporary discontinuation of smoking were not recorded. Current smokers were asked whether they inhaled not at all, somewhat or deeply, whether they smoked filter tips and, if so, when they began smoking filter tips. Similar questions were asked on use of cigars and pipes, except that the questions on filter tips were omitted. In Boston and Manchester subjects were asked about the use of cigarillos. In Nagoya subjects were asked, instead, about the use of the kizami type of pipe, which has a long and thin tube.

This presentation is restricted to the 1,125 subjects in Boston, 1,284 in Manchester and 878 in Nagoya who could be classified as nonsmokers, ex-smokers or current smokers of <1, 1 or ≧2 packs of cigarettes per day. Additional subjects were excluded from specific analyses because they did not respond adequately to the pertinent items on the questionnaire.

Results are expressed primarily in terms of the relative risk, which is an estimate of the ratio of the bladder cancer incidence rate of persons in a given exposure category to the rate for the reference category. Except when stated otherwise, the summary relative risks presented are simultaneous maximum likelihood estimates[15] with stratification for age (<65, 65 to 74 and ≧75 years).

RESULTS

A history of smoking cigarettes was associated with an elevated rate of bladder cancer in all 3 areas and in both sexes (table 1). Among men the relative risk in persons who had ever smoked compared to nonsmokers was approximately 2 in each study area. Among women the relative risk varied more, being higher in Boston and Nagoya, and lower in Manchester. For the 3 areas combined the relative risk was 1.9 in men and 2.4 in women (area and age were controlled in these estimates). Table 1 also gives values for the population attributable risk per cent,[16,17] which is in this instance the estimated proportion of all cases of bladder cancer in a group attributable to its experience with cigarette smoking. The population attributable risk per cent depends on the relative risk and the frequency of exposure. The values range from a low of 14 per cent in Manchester women to a high of 56 per cent in Boston women.

Intensity. The relative risk increased regularly with the number of packs per day smoked (table 2). Men who currently smoked ≧2 packs per day had a relative risk estimated as 4.7 in Boston, 4.0 in Manchester and 2.8 in Nagoya. In none of the study areas were sufficient women interviewed to obtain satisfactory estimates of relative risk for heavy smokers. Boston and Nagoya women who were current smokers of <1 or ≧1 packs per day appeared to have substantially higher relative risks than the corresponding groups of men. In Manchester the relative risks were similar in men and women who smoked <1 pack a day and were somewhat higher in men than in women who smoked ≧1 packs per day. In all 3 study areas ex-smokers had a relative risk similar to that of light smokers or nonsmokers. Boston women who had stopped smoking had a relative risk of 3.4. Otherwise, ex-smokers had lower relative risks in the range of 0.7 to 1.8. Relative risks standardized[18] for current intensity of cigarette smoking (as well as for age) were 2.6, 2.0 and 2.3 in Boston, Manchester and Nagoya men, respectively, and 3.0 and 1.7 in Boston and Manchester women. (There were too few female smokers in Nagoya for satisfactory standardization.)

The effects of cigarette smoking on the risk of bladder cancer varied with age at interview (table 3). In Boston and Manchester the strongest associations were observed in relatively young subjects. In Nagoya men <65 years old, on the other hand, the associations were weak compared to those in older men. A higher relative risk was observed in Nagoya women <65 years old compared to older women but the difference was modest and the number of subjects was small. Since the incidence rate of bladder cancer increases sharply with age[19] a given relative risk might not correspond to the same difference in incidence rate at different ages. Because our studies were based on geographically defined populations it was possible to estimate not only the relative risk but the actual incidence rate of bladder cancer in groups defined according to smoking history and age. However, trends in incidence evaluated in this way did not suggest a simple explanation of the divergent trends in relative risk by age.

Inhaling. The reported degree of inhaling was associated with risk among cigarette smokers. With control of current intensity of cigarette smoking (<1, 1 or ≧2 packs per day) as well as age,

TABLE 1. *The association of a history of cigarette smoking and bladder cancer: relative risk and population attributable risk per cent*

	Boston	Manchester	Nagoya
Men:			
Relative risk (95% confidence interval)	1.9 (1.3–2.8)	2.2 (1.4–3.5)	1.7 (1.1–2.9)
Population attributable risk %	44	46	34
Women:			
Relative risk (95% confidence interval)	4.2 (2.5–7.1)	1.3 (0.8–2.0)	4.3 (2.0–9.2)
Population attributable risk %	56	14	24

TABLE 2. *Numbers of cases and controls, and relative risk according to current frequency of cigarette smoking*

Frequency (packs/day)	Men			Women		
	Cases	Controls	Relative Risk	Cases	Controls	Relative Risk
Boston						
Nonsmoker	53	84	1.0	49	88	1.0
Ex-smoker	191	206	1.5	50	27	3.4
<1	25	28	1.4	18	9	4.3
1	91	48	3.2	48	18	6.2
≧2	67	25	4.7			
Manchester						
Nonsmoker	28	67	1.0	63	99	1.0
Ex-smoker	150	207	1.8	26	69	0.7
<1	85	109	1.9	40	42	2.1
1	104	86	3.2	26	31	2.2
≧2	31	21	4.0			
Nagoya						
Nonsmoker	24	77	1.0	45	131	1.0
Ex-smoker	28	92	1.0	3	2	—
<1	47	94	1.6	11	8	4.4
1	92	140	2.1	7	5	4.2
≧2	33	39	2.8			

TABLE 3. *Relative risk* according to cigarette smoking history and age*

Age (yrs.)	Men					All Women Smokers
	All Smokers	Ex-Smokers	Current Smokers (packs/day)			
			<1	1	≧2	
Boston						
<65	3.1	1.7	2.2	4.0	8.9	23.5
65–74	2.3	1.8	2.0	4.3	2.8	5.4
≧75	1.3	1.2	0.9	1.8	1.8	1.8
Manchester						
<65	4.9	4.4	4.4	5.5	6.2	9.1
65–74	1.4	1.1	1.1	2.6	3.4	0.7
≧75	1.4	1.1	1.5	2.2	—	1.0
Nagoya						
<65	1.1	0.4	1.1	1.3	1.6	5.5
65–74	2.3	1.5	1.9	2.8	4.4	3.5
≧75	2.3	1.3	2.0	3.4	3.3	3.4

* Ratio of incidence rate of bladder cancer in indicated exposure category to the rate in nonsmokers in the same age group.

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men who inhaled deeply had a relative risk of 1.4 (0.8 to 2.3, 95 per cent confidence interval) in Boston, 1.3 (0.8 to 1.9) in Manchester and 1.4 (1.0 to 2.1) in Nagoya, compared to men who reported that they inhaled somewhat or not at all. The corresponding values for women were 2.4 (0.7 to 7.8) in Boston and 0.7 (0.3 to 1.8) in Manchester. (There were too few Nagoya women who smoked for satisfactory analysis of degree of inhaling.) Men who smoked ≧2 packs of cigarettes per day and inhaled deeply had a relative risk compared to nonsmokers of 6.6 (3.0 to 14.5) in Boston, 8.1 (3.0 to 21.5) in Manchester and 2.6 (1.1 to 6.5) in Nagoya.

Because the numbers of exposed women were relatively small, further analysis of the relationship of smoking and bladder cancer was limited to men.

Duration. Except for temporary periods of discontinuation, the duration of smoking among current smokers who were a given age at interview depended on the age at which smoking started. Table 4 presents relative risks in male current smokers according to age when cigarette smoking was started. These values were adjusted for the current intensity of smoking. Nearly all smokers had begun to smoke before age 25 years. Regular decreases (or increases) in risk with increasing age at starting were not observed.

It was indicated previously that ex-smokers had somewhat lower relative risks than current smokers. With control of the average intensity of smoking during the period in which the subject smoked the relative risk in male ex-smokers compared to current smokers was estimated as 0.5 (0.4 to 0.8) in Boston, 0.7 (0.5 to 0.9) in Manchester and 0.5 (0.3 to 0.8) in Nagoya. The relationship between time since stopping and risk was weak and inconsistent among the study areas. In Boston men who had stopped smoking ≧15 years before the interview had a relative risk of 1.2 compared to those who had stopped more recently. In Manchester and Nagoya the respective values were 1.0 and 0.9.

Filters. The effect of current use of filter tips was evaluated among men. The relative risk estimates were adjusted for current intensity of smoking. Compared to smokers not currently using filters, users had a relative risk of 1.3 (0.7 to 2.3) in Boston, 1.2 (0.8 to 1.8) in Manchester and 1.0 (0.5 to 1.9) in Nagoya. There was little difference in risk between those who had used filters for ≧10 years versus a shorter period.

Pipes and cigars. Analysis of the effects of pipe and cigar smoking was limited to men who were not current smokers of cigarettes.

Compared to men who had not smoked pipes, men in Boston who had smoked pipes had a relative risk estimated as 1.2 (0.8 to 1.8), with control of the average intensity of cigarette smoking among ex-smokers. Among men who had never smoked cigarettes those who had ever smoked pipes had a relative risk of 1.7 (0.8 to 3.6) and current pipe smokers had a relative risk of 1.8 (0.7 to 4.9). In Manchester the relative risk associated with pipe smoking was 1.2 (0.8 to 1.9). Among men who had never smoked cigarettes the relative risk associated with ever smoking pipes was 3.9 (1.3 to 11.8) and with current smoking of pipes it was 8.6 (2.1 to 35.6). In Nagoya only 2 subjects reported smoking western style pipes. However, a number of men had smoked kizami pipes. The relative risk associated with smoking kizami pipes was 1.3 (0.5 to 3.5). There were not enough kizami smokers among nonsmokers of cigarettes to obtain a relative risk estimate for that group.

Two subjects reported smoking cigars in Nagoya. Cigar smoking was more common in Boston and Manchester but there was virtually no association of that habit with risk of bladder cancer. Three cases and five controls were current smokers of cigarillos.

TABLE 4. *Numbers of cases and controls, and relative risk according to age when smoking began among current smokers*

Age (yrs.)	No. Cases	No. Controls	Relative Risk*
		Boston	
<15	53	27	1.0
15–19	89	46	1.1
≧20	36	25	1.0
		Manchester	
<15	73	78	1.0
15–19	92	80	1.3
≧20	39	48	0.9
		Nagoya	
<20	59	68	1.0
≧20	109	193	0.7

* Adjusted for age and current intensity of cigarette smoking.

DISCUSSION

A substantial amount of evidence has accumulated in support of a relationship between cigarette smoking and the development of bladder cancer. A number of case-control studies have been positive. Generally, smokers have appeared to suffer bladder cancer at 2 to 3 times the rate of nonsmokers. Risk has been found to increase with increasing frequency of consumption of cigarettes and with the degree of inhaling.[1-7] Followup studies of tobacco users and nonusers[8-11] have given results consistent with those of case-control studies.

This study confirms and extends previous observations. In all study areas men who had smoked cigarettes had about twice the bladder cancer rate of nonsmokers. This finding is of particular interest in view of the variation in bladder cancer rates among the areas studied. The incidence of bladder cancer in Nagoya is only about half the rate in Manchester and one-third the rate in Boston (unpublished observations). The relative risk associated with smoking varied more for women than for men and the female risks were the higher in 2 of the 3 study areas. Over-all, however, the relative risk was similar for the 2 sexes. Cigarette smoking generally has not been viewed as a strong risk factor for bladder cancer. However, our results suggest that the risk is high for heavy smokers who inhale deeply. Reports by subjects of their own inhaling practices may be poor indicators of the amount of smoke that is absorbed.[20] Therefore, the increase in risk in those who inhale deeply may be even greater than that observed.

In our study risk was not clearly related to increasing duration of smoking (as measured by age at starting). Hirayama observed a weak inverse relationship between duration (as measured by age at starting) and risk.[21] Howe and associates,[3] and Wynder and Goldsmith[5] observed, in contrast, increases in risk with increases in the reported number of years of smoking. However, in the latter 2 studies the analyses of duration appear to have been based on a mixture of current and ex-smokers, of whom the ex-smokers can be assumed to have been at lower risk. The trend of risk with duration in these 2 studies is, therefore, likely to have been, at least in part, a consequence of a higher proportion of ex-smokers among those who smoked for shorter compared to longer durations. In fact, the strength of the relationship between duration of smoking and risk, independent of the difference between current and ex-smokers, will probably be difficult to measure with reasonable precision because the variation in age at starting to smoke is small compared to the long period that elapses between the start of smoking and the diagnosis of most cases of bladder cancer. Moreover, errors in reported age at starting might easily obscure a small gradient in risk.

We found no obvious relationship between time since discontinuation of smoking and reduction of risk. Howe and associates,[3] and Wynder and Goldsmith[5] reported decreases in risk with increasing time since stopping. In the data of Howe and associates the decrease was small—a relative risk (compared to current smokers) of 0.63 in those who stopped 2 to 15 years ago and 0.55 in those who stopped >15 years ago.[3] (These relative risks were derived from the logistic coefficients in their paper.) The difference between these figures was well within the range expected on the basis of chance variability and these results seem consistent with our own. Wynder and Goldsmith

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reported a larger decrease in risk with time since cigarette smoking was stopped.[5] However, their results were not adjusted for intensity of smoking and those who stopped smoking relatively long ago, that is relatively soon after starting, may well have been comparatively light smokers and at lower risk for that reason.

Neither we nor Wynder and Goldsmith[5] found much difference in bladder cancer risk between male smokers who had used filters for a long period and those who had not. Howe and associates observed a lower risk in smokers of filter cigarettes compared to smokers of nonfilter cigarettes,[3] although the difference is readily attributable to chance.

In our centralized review of slides we found virtually no difference in histologic features of bladder cancer in groups of subjects with different cigarette-smoking histories.[14] Howe and associates observed a substantial increase in bladder cancer risk among pipe smokers.[3] Lockwood,[6] and Williams and Horm[22] also observed positive associations, although weaker ones, between pipe smoking and bladder cancer. There was little over-all relationship of pipe smoking to risk in our study but an association was apparent among men who reported not smoking cigarettes. Except for Lockwood's report,[6] there is little evidence to suggest that cigar smoking is a risk factor for bladder cancer.[2,3,22]

The lack of consistency in the observed effects of filters, pipes and cigars is not surprising. It is probably true that any change in risk related to each of these exposures is small. Moreover, each of these exposures is likely to be associated with cigarette smoking in ways that are complex and not readily controlled. For example, smokers of filter cigarettes might inhale more (or less) frequently than smokers of plain cigarettes, or leave butts of different lengths. Even if all of the relevant characteristics were recorded, measurement errors could make such interrelationships difficult to disentangle. One approach that may be helpful in some circumstances would be to restrict analyses of one exposure to subjects never exposed to other, potentially related exposures. Thus, pipe smoking could be evaluated, as in our study, among people who never smoked cigarettes.

In previous case-control studies in the United States it was estimated that 39 to 48 per cent of bladder cancer in men and about 30 per cent of the disease in women were attributable to cigarette smoking patterns.[2,5] The corresponding value in men in the United States in our study is similar to the previous results, while our value in women is higher than the previous figures. Recently, Moolgavkar and Stevens estimated that about 85 per cent of bladder cancer deaths in men in the United Kingdom and about 27 per cent of those in women were attributable to smoking.[23] These values are about twice as high as those we obtained for subjects in the United Kingdom. Their value for men also is higher than any others reported for men in the United States or Canada.[3]

Moolgavkar and Stevens attempted to explain the discrepancy between their results and those for American men on the basis of 1) higher consumption of cigarettes in the United Kingdom and 2) lack of precision in previous estimates. The latter explanation is unlikely to account for much of the discrepancy, since the previous estimates are, as a group, rather different from the estimate of Moolgavkar and Stevens. At least some of the discrepancy is likely to be the result of the method used by Moolgavkar and Stevens. These authors estimated the relative risk in smokers compared to nonsmokers and the population attributable risk per cent from population data by use of a mathematical model, and not by observations on smoking and bladder cancer in the same individuals. In this model it was assumed that relative risk among smokers is a multiplicative function of cumulative dose. Such a function is much steeper than observed dose-response curves for cigarette smoking and bladder cancer in men.[24] Consequently, the overall relative risk experienced by smokers and the population attributable risk per cent may have been overestimated by Moolgavkar and Stevens. On the other hand, most estimates of relative risk and population attributable risk per cent derived from case-control studies are likely to be underestimates. Information obtained at the interview is unlikely to be an entirely accurate reflection of long-term cigarette consumption patterns. Such random errors lead to underestimates of all measures of risk. The extent of this underestimation is unknown.

Mr. J. Barrington Bates performed the computer programming.

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